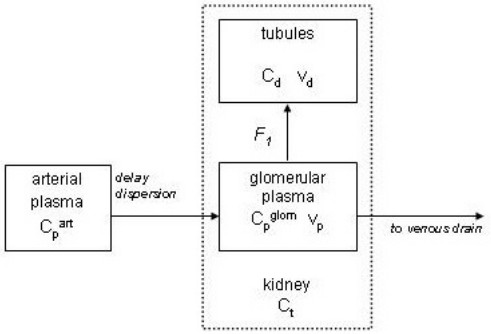
Accurate and precise measurement of renal filtration and vascular parameters using DCE-MRI and a 3-compartment model.

P. S. Tofts[1], M. Cutajar[1,2], I. Mendichovszky[3], and I. Gordon[2]
[1]Imaging Physics, Brighton & Sussex Medical School, Brighton, East Sussex, United Kingdom, [2]Radiology and Physics, UCL Institute of Child Health, London, London, United Kingdom, [3]University of Manchester, Manchester, United Kingdom

Hypothesis: A recent compartmental model[1,2] of DCE-MRI can provide precise and accurate measurements of renal filtration, blood flow and blood volume, and hence be reliable enough for clinical studies. Precision would be estimated from repeated measurements; accuracy by comparison with published normal values.
Introduction: A 3-compartment model[2] fits DCE data with small residuals. Two modes have been described: *uptake mode* (for data up to 90s, when efflux is ignored), and *complete mode* (for longer time-series, when efflux is allowed). Cortical and parenchymal ROI's have been studied.
Methods: **MRI:** 15 normal subjects were imaged before and after injection of 0.05 mmole/kg of Gd-DTPA, on a Siemens 1.5T Avanto imager, using a TIM 32 channel body phased array coil. A spoilt gradient echo 3D sequence had TR=1.6ms, TE=0.6ms, FA=17°. 18 contiguous 7.5mm slices were collected every 2.5s, with in-plane resolution 3.1 x 3.1mm, covering both kidneys. Subjects were imaged a week later, giving a total of 60 normal kidney curves.
Compartmental Modelling: The 3-compartment model[1,2] was simplified to exclude efflux:

$$C_p^{glom}(t) = C_p^{aorta}(t) \otimes g(t) = \int_0^t C_p^{aorta}(t-\tau) g(\tau) d\tau$$

$$C_t(t) = v_b(1 - Hct^{small}) C_p^{glom} + K^{trans} \int_0^t C_p^{glom}(\tau) d\tau$$



C_d, C_p^{aorta}, C_p^{glom}, C_t are the time-dependent concentrations in v_d, aortic plasma, glomerular plasma, and kidney tissue respectively. v_p, v_b and v_d are the fractional volumes of glomerular plasma, glomerular blood and the distribution space for tracer extracted from the blood (principally the tubules). The delay and dispersion for plasma-borne tracer travelling from the aorta to the glomeruli are described by the Glomerular Impulse Response Function (GIRF) g(t). F_1 is the tracer extraction rate per unit volume (mmole min^{-1} mL^{-1}) from the glomerular plasma by the kidney; $F_1=K^{trans} C_p^{glom}$; K^{trans} is the transfer constant[3] from glomerular plasma to kidney (GFR per unit volume of tissue).
MRI modelling: There were 4 free parameters: v_b, K^{trans}, and 2 delay and dispersion parameters which defined the GIRF. Three GIRF shapes were investigated: instant exponential decay; delayed exponential decay; and delayed gaussian. Blood flow F was estimated from the peak, and also using $F=v_b/MTT$ (MTT=mean transit time). Filtration Fraction $FF=K^{trans}/F$. Perfusion mode (using tissue data up to the post-bolus dip) enabled F and v_b to be estimated with minimal influence of filtration.
MRI analysis: AIF's were found from the descending aorta. Blood T_{10} =1.4 s; parenchyma T_{10} =1.2 s. Relaxivity r_1=4.5 s^{-1} mM^{-1}. Hct = 41%. Kidney volume was measured from ≈8 slices in each kidney. Normal group (n=15) mean and sd were found. Instrumental sd was found from the repeats using Bland Altmann analysis. Body Surface Area was estimated from BSA (m²) = 0.0235 Height(cm)$^{0.422}$ Weight(kg)$^{0.514}$. [4] Standardised kidney volumes (for BSA=1.73m^2) were calculated.
Normal single kidney volume V_{kid} was estimated from the published normal value of mass m=150g as follows: $V_{par}=m/\rho$; $V_{kid}=V_{par}/(1-\alpha v_b)$ (V_{par}=total volume of parenchyma (excluding blood); ρ=parenchymal density=1.03; α=fraction of blood that drains out when kidney is excised and weighed (estimated α=0.9±0.1)); v_b=0.35 (ref [5]). Thus V_{kid}=213±11 mL.
Results: Delayed exponential and gaussian GIRF's fitted better (rms residual ≈3-4%) than instant exponential; gaussian values are shown in the table. Cortical ROI's gave higher values of filtration, and lower MTT's, than parenchyma, as expected. However parenchymal v_b (44%) and F were unexpectedly higher than cortical v_b (35%) and F. Perfusion mode gave better fits that uptake mode (residuals ≈1% lower); however reproducibility and perfusion parameters were the same.

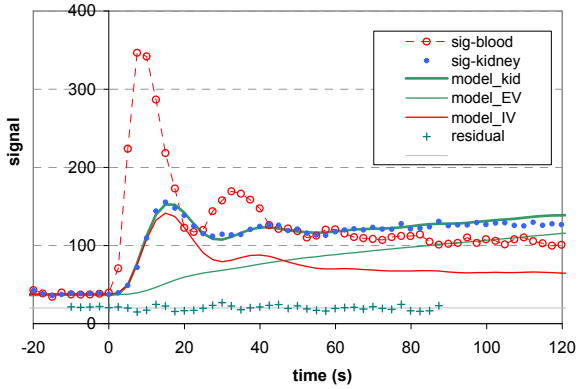


Figure: uptake mode fit to parenchymal ROI for 90s

		MRI normal mean±sd	instrumental sd	literature normal
filtration (min^{-1})	K^{trans}	0.25±0.05	0.04 (15%)	0.28(a)
Mean Transit Time (s)	MTT	5.9±0.7	0.4 (6%)	6.5 [6]
blood volume (%)	v_b	44±10 (b)	7 (17%)	35%(c) [5]
blood flow mL min^{-1} (100 mL)$^{-1}$	F	495±153 (d)	62 (12%)	258(e,f)
filtration fraction (%)	FF	8.9±1.6	0.7 (8%)	15-20 [7]
absolute kidney volume (mL)	V_{kid}	230±28	-	213
standardised kidney volume (mL)	V_{kid}^*	214±20	-	213
GFR (mL min^{-1})	GFR	115±27	-	120 [7]

(a) = GFR/($2V_{kid}$*) (b) right cortical v_b=35% (c) CT method[5] (d) right cortical F = 435 ± 110 (e) using total RBF=1.1 L min^{-1} [7] (f) cortical F = 416 (Case Kid Int 1978;13:236)
Table: analysis of parenchymal ROIs in uptake mode

Discussion and Conclusions:
1. Three renal physiological parameters (filtration, MTT and blood volume) when measured using MRI, have instrumental SD ≈ 6-17%; thus realistic group and individual differences might be reliably detected. Clinical studies would demonstrate sensitivity of these parameters to physiological change.
2. The accuracy of the filtration values (K^{trans}) is excellent (see table).
3. Mean transit time MTT is precise, unaffected by T_{10}, Hct or r_1, possibly as sensitive to physiological changes as blood flow, and a good biomarker candidate.
4. The accuracy of *parenchymal* blood volume v_b (and hence blood flow F and filtration fraction FF) is disappointing. v_b appears to be too high, giving high F and low FF. Similarly high parenchymal F values from DCE MRI have been reported by Sourbron[6] (plasma flow = 220; F = 370).
5. Right *cortical* v_b and F are accurate. Left cortical values showed an inexplicable and significantly higher v_b and F (p<1E-8).
6. Possible causes of parenchymal perfusion parameter inaccuracy are naive modelling of the medullar vasculature, or systematic error from assumed T_{10}, FA, Hct or r_1 (a small vessel Hct=30% would give reduced v_b=37%).
7. Tubular relaxivity r_1 may be as low as 50% of the assumed in-vitro value[8] and would increase estimates of K^{trans} but not v_b or F.
8. Our measured standardised single kidney volume (214 mL) agrees with an estimate from the published mass (150g) that takes account of the large blood volume; it differs from the value obtained using the naïve assumption of unit density (this gives 150 mL).
9. Improved movement correction might improve the repeatability.

References: 1. Tofts ISMRM 2008; 454 2. Tofts ISMRM 2009; 408 3. Tofts JMRI 1999;223 4. Gehan EA Cancer Chemotherapy Rep 1970;54:225
5. Tsushima Am J Kid Dis 1999;33:754 6. Sourbron Invest Radiol 2008;43:40 7. Eaton *Vanders Renal Physiology* 2009 8. Shuter Magn Res Imag 1996;14:243